from bone marrow.

28. The method of claim 25, wherein said administering is by injecting.

29. The method of claim 25, wherein said method improves cardiac function as measured by the cardiac ejection fraction.

30. The method of claim 25, wherein said method causes an angiogenic response.

REMARKS

The Invention

The invention features methods of treating damaged or scarred myocardial tissue by implanting differentiated or undifferentiated mesenchymal stem cells to improve cardiac function.

Support for Amendments

The title has been amended to better reflect the subject matter of the invention. Claim 2 has been amended to depend from claim 25. The subject matter covered by the combination of claims 1, 2, and 25 is identical in scope to that of claims 1 and 2 prior to amendment. Therefore, the amendment to claim 2 and the addition of claim 25 does not introduce new matter relative to the scope of the claims as originally filed. Support for the amendment to claim 3 is found in the specification at page 22, lines 9-10. Support for the amendment to claim 7 is found at page 9, lines 2-8. Support for the amendment to claim 12 is found at page 26, lines 16-20. Claims 2, 4, 5, and 7 have been amended to depend from claim 25. These amendments are made to expedite prosecution and do not reflect a belief by Applicants that the claims as filed were unpatentable prior to amendment.

Claims 25-30 have been added to more distinctly point out the subject matter which the Applicants regard as their invention. The new claims do not alter the subject matter of the claims as originally filed. Support for new claims 25-30 is found at page 3, lines 4-7, and page 4, lines 4-9.

No new matter is introduced by these amendments.

A "marked up" version of the claims showing the changes made and an appendix of the claims as pending are attached.

The Office Action

Claims 1-13 are pending in this application. Claims 2-9, 12, and 13 stand rejected for indefiniteness under 35 U.S.C. § 112, second paragraph. Claims 1-13 are further rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. 5,736,396. These rejections are addressed below, in the order in which they appear in the Office Action.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 2-9, 12, and 13 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner rejects claims 2, 4-9, and 13 for indefiniteness and asserts that the claims imply additional active steps which are omitted. Applicants respectfully traverse this rejection. The source of mesenchymal stem cells and methods for preparation are obvious to a practitioner skilled in the art. Furthermore, the routine, intervening steps are not material to patentability and are rightly omitted. Notwithstanding, in order to expedite prosecution, not for reasons related to patentability, Applicants have amended the claims.

Claim 2 has now depends from claim 25, which recites the step of *ex vivo* culture. Claims 4, 5, 7-9, and 13 have been amended to depend from claim 2. Claim 6 is drawn to a specific source of the mesenchymal stem cells rather than a method or further step that

must be performed. Therefore, Applicants respectfully submit that the rejection of claim 6 is improper and should be withdrawn. Accordingly, claims 2, 4-9, and 13 should now be allowable.

Claims 3 and 12 stand rejected as indefinite on the ground that they appear to omit some active steps by failing to specify what parameters are evaluated or what steps are required to evaluate the effects as claimed. While Applicants disagree, to expedite prosecution, claims 3 and 12 have been amended to include specific criteria to be evaluated. Claim 3 recites the induction of an angiogenic response and claim 12 recites increased cardiac function as measured by an improvement of ejection fraction. A skilled artisan in the field of treatment of cardiac disease can readily identify an appropriate method to measure ejection fraction or increased angiogenesis in the species under study. Accordingly, claims 3 and 12 should now be allowable.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-13 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. 5,736,396 (hereinafter, "the '396 patent"). Specifically, the Examiner asserts that the '396 patent anticipates the method of the present invention by teaching a method of treating an individual in need of mesenchymal cells of myogenic lineage by administering to the individual a composition of mesenchymal stem cells which have been induced to differentiate *ex vivo*. Applicants respectfully disagree.

The '396 patent does not teach the use of mesenchymal stem cells or cells derived from mesenchymal stem cells for treatment of damaged or scarred myocardial tissue, as is claimed by the present application. The '396 patent includes examples of *ex vivo* differentiation of mesenchymal stem cells into osteogenic, chondrogenic, stromagenic, and myogenic cell types and describes the use of these cells for "treating an individual in need of mesenchymal cells." The only guidance in the '396 patent regarding conditions that may be treated using differentiated mesenchymal cells is found at column 5, lines 13-

28. Specifically, the '396 patent refers to injecting cells into the site of a skeletal defect (lines 16-17), or to treat "metabolic bone disease, skeletal dysplasias, cartilage defects, ligament and tendon injuries and other musculoskeletal and connective tissue disorders" (lines 26-28). By contrast, the present claims are drawn to the treatment of damaged or scarred myocardial tissue. Unlike the present invention, the '396 patent never considers the use of differentiated mesenchymal stem cells for treatment of injured myocardial tissue. Accordingly, this rejection should be withdrawn.

Enclosed is a petition to extend the period for replying for three months, to and including July 17, 2001. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 17, 2001

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Version With Markings to Show Changes Made

In the Title:

[CARDIAC FUNCTION BY] MESENCHYMAL STEM CELL TRANSPLANTATION INTO DAMAGED MYOCARDIUM

In the Claims:

2. The method of claim [1] 25, wherein at least one mesenchymal stem cell has been induced to differentiate into a cardiomyogenic cell prior to administration.

3. The method of claim 1, wherein [at least one mesenchymal stem cell integrates into a capillary wall in damaged or scarred myocardial tissue] said method improves cardiac function by causing an angiogenic response.

4. The method of claim [1] 2, wherein said mesenchymal stem cells have been cultured for at least 7 days.

5. The method of claim [1] 2, wherein said mesenchymal stem cells have been co-cultured with cardiomyocytes.

7. The method of claim [1] 2, wherein said differentiation is induced by contacting said mesenchymal stem cells [are exposed to] with 5-azacytidine or an analog thereof, prior to administration.

12. The method of claim 1, wherein said method improves cardiac function as measured by the cardiac ejection fraction.